CHAPTER II: HERBS AND OTHER DIETARY SUPPLEMENTS

Overview of Dietary Supplements

I'm going to try to give you a flavor of what it's like to be doing research in an area like dietary supplements. I'll give you some background on what supplements are and maybe by extension you'll realize what supplements aren't. I'll also try to give you some idea about the array of research issues that we contend with, with respect to dietary supplements in large part because the field is so very broad, and what constitutes a supplement is a very big definition. Who takes supplements? About 2/3 of people take them.

The first thing I wanted to do though is to put us all on the same page. It's not as if dietary supplements appeared on the planet one day in 1994. It just feels like that. In 1994, Congress passed, and the president signed, a piece of legislation called the Dietary Supplement Health and Education Act (DSHEA) of 1994. This was a piece of legislation that was some years in the building, and it capitalized on a number of aspects of then-current American thinking about things like the availability of health care, taking charge of your own health, looking toward relatively inexpensive ways of dealing with health problems, and being frustrated with the standard American academic medical model. It's no big surprise that some of the same issues that created an enthusiasm for complementary and alternative medicine were also there to create enthusiasm for dietary supplements. These are not separate from one another. You will discover, if you haven't already, that there are areas of overlap, and indeed, supplements have been regularly used as part of the armamentarium that people who are interested in integrative medicine use. In any event, in 1994, the DSHEA was passed with a few particular pieces of information in mind. One was that American consumers were guaranteed access to products in this dietary supplement category. Why was that even an issue? As the legislation was coming to a close, and as the legislators and lobbyists in 1994 were putting the final touches on this, one of the things that happened was that there was a groundswell of enthusiasm and concern about supplements in the U.S. Enthusiasm for the availability of these relatively inexpensive, relatively time-tested, and relatively safe—and these are all terms that were

in use at the time—supplements. They will, as you'll discover, be features of some but not all supplements, but there was a lot of enthusiasm. There was also a lot of marketing going on, and I don't know if any of you remember a television commercial from 1994. It was a public service piece; I don't who funded it. But there was this character in his bathroom, opening the medicine cabinet, and all of a sudden, two big guys wearing "Supplement Police" jackets came into his bathroom and slammed him up against the wall. The message was that if Americans didn't do something about the attitude of the Federal government toward the regulation of supplements, we were going to lose everything— vitamins, minerals. It's assumed that that was the truth. I don't really think it was the truth, but there was a lot of concern at the time that unless Congress passed this legislation that Americans would be denied access to their favorite dietary supplement products.

So there began the biggest campaign of letter writing and contacting of Congressmen in the U.S. in both houses. The campaign was bigger than the letter-writing campaign that went on before and during the Vietnam War. It was quite a remarkable piece of work that was completed. When it was passed, the Act was intended to ensure that Americans had access to products in the category. What products? It defined dietary supplements, and I'll give you a definition and some examples in a little bit. It established what the regulatory arms of the Federal government could do and couldn't do in regulating dietary supplements. It created a framework for what the U.S. Food and Drug Administration (FDA) could do. Regulations for dietary supplements are much more like food regulations than they are drug regulations. The Act also established what a label for a dietary supplement should look like. The last thing that it did was to establish the Office of Dietary Supplements at the National Institutes of Health under the Office of the Director, and that's the organization that I run. It was intended to be an independent, science-driven office. The Act actually more or less defined what the Office of Dietary Supplements should be doing and that is to develop a scientific basis in order to inform American consumers about the benefits of dietary supplements. That's really only 1/2 of a larger picture. The picture always has to contain information about benefits, risks, harms, and potential good things, for example adverse events versus efficacy. We don't

think of one without the other. It doesn't mean that all dietary supplements by definition are great or that all dietary supplements by definition are harmful. That's not true. But we cannot make the assumption, without evidence, that dietary supplements are both effective and safe. So that's what we were charged with doing.

The DSHEA defined dietary supplement as a product (other than tobacco) intended to supplement the diet, ingested, bearing one or more of the following dietary ingredients: a vitamin; a mineral; an amino acid; or an herb or other botanical. Do all of those sound like they're dietary ingredients to you? Vitamins, minerals, and amino acids are certainly of dietary origin, and they're in all of the foods that you eat, but herbs and other botanicals aren't We can take herbs as part of our diet, but not everybody does. The Act went a little further and included some botanical ingredients that really aren't part of anybody's diet, at least not in the U.S.

The Act went on to say that the product could be a dietary supplement for use to supplement the diet by increasing the total dietary intake. What does that mean for you? What it means in practice is that, for example, if you buy a dietary supplement that contains vitamins, you're supplementing something that you're already taking in your diet—vitamins and minerals. What about St. John's wort? You don't normally take that in your diet. So supplementing in that example means supplementing over zero as opposed to supplementing over normal dietary intake. The DSHEA also went on to say that it had to be a concentrate, a metabolite, a constituent, an extract, or a combination of any of the ingredients described above. In practice, that's turned out to be a very difficult thing to get your arms around. It also went on to say that the product was intended for ingestion in the form of a capsule, a powder, a soft gel, or a gel cap. That means it needs to look like a drug. But it can't be represented as a conventional food or as the sole item of a meal or the diet. So you've got this situation in which dietary supplements are intended to look like drugs but are going to be regulated as foods. That creates something of a dilemma. It's not impossible to deal with, I assure you, but it does create some dilemmas for people. Particularly, I think, for consumers who look at bottles of dietary supplements on the pharmacy shelf, as well as on the natural food store shelf or the

supermarket shelf, and the bottles look like the drugs that are sitting on the shelf next to them (they cannot be put on the same shelf with their "cousin" drugs because they are intended to be separated from drugs).

Well, for the purposes of simplicity, let's think of 3 kinds of ingredients that you can find in dietary supplements: botanical ingredients; nutrient ingredients; and a rather amorphous category of other dietary substances. This gives you some idea of the kinds of ingredients that are present in dietary supplements. They include the familiar vitamins and minerals that are part of many foods. They include antioxidants, which you also can find in a great many foods. It should be noted that the term antioxidant is not very specific. It includes a great many different kinds of categories of ingredients. It includes things like creatine and carnitine. These are single metabolic intermediates. They're molecules that serve a function in particular metabolic pathways. Then there are products like lutein, lycopene, and phytoestrogens that are present in a host of foods that you're familiar with. They also include some of the foods themselves where an extract of soy or an extract of garlic is sold as a dietary supplement. You've surely heard of omega-3 fatty acids that come from fish, so not all dietary supplements are botanical in origin. This category of dietary supplements does contain botanical ingredients, and you're familiar with some; I've only provided a few examples here: St. John's wort; echinacea; and ephedra. There are many others. It also includes some things that are in this category for reasons that some now find a little difficult to understand. These include the prohormones like androstenedione.

Some of these ingredients have gained some excitement and positive press, and others like androstenedione and ephedra have had a very much different fate, and the press around them is dramatically negative. I think one of the things that you should know about the dietary supplement marketplace in the U.S. is that it's almost unique in one respect; unlike the sale of dietary supplements in other countries where vitamins are sold as vitamins and where St. John's wort is sold as a phytomedicine (as an almost purified drug in Germanic countries and Europe), the U.S. has the interesting market niche of products that are sold in combination. Therefore, a product that can be sold for athletic

performance enhancement will contain vitamins and minerals, and it will contain creatine and carnitine, and it might also contain ginseng. It will certainly contain ephedra or something that looks like that, and it will probably also contain androstenedione. We like combinations of things, and this is a fairly unusual circumstance when compared with the rest of the world. In any event, dietary supplements cover a multitude of ingredients. It's a big market.

In 2001, the sales of dietary supplements from a number of different sources approached $18 billion in the U.S., and that was after several years of really very dramatic growth, particularly since the creation of the DSHEA in 1994, when there was a huge increase in the sales of dietary supplements. In fact, as the decade ended, sales leveled off. In the last few years, sales have crept up rather than skyrocketed as they had for the previous 5 or 6 years. This slide is intended to give you an idea of the major categories and their relative contribution to the sales stream. Vitamins total almost $6 billion, minerals $1.2 billion, and herbs and botanicals $4 billion in sales in 2001. There is another large category of other supplements that often contains the combination of products that I gave examples of before, and then there is sports and nutrition as another major category.

For comparison, sales of prescription drugs in the U.S. totaled $150 billion dollars in 2001. Clearly, supplement sales are low in comparison, but the amount of money that has been spent on supplements is not trivial.

How are supplements regulated? I gave you some clues about this earlier. I did say that food rules apply. What that means in practice is that just as with food, supplements, by law, are presumed safe, based on their history of use in humans. You probably can think of some very good reasons why that's true and also why that should not necessarily be held true in every case. If an ingredient was on the market as a dietary supplement in 1994, and as I said, they didn't just appear in the marketplace in October of 1994, it was there before. If it was on the market as a supplement before the law was passed, then it was grandfathered in. This meant that the FDA had no role in the evaluation of the product, the ingredient, its efficacy, its safety, or how it was manufactured. For those

products, manufacturers do not have to provide the FDA with evidence of efficacy or safety before marketing. It is assumed that they have that information in their files and that they had that information either from work that they've done themselves or that is historically available. However, manufacturers are not obliged to provide that information to the FDA. Incidentally, the FDA wouldn't have the resources to be able to deal with it even if it were available to them. The FDA really has one major role in the regulation of dietary supplement ingredients, and that is that once a product is on the market, the FDA has to prove that the product is unsafe in order to restrict it or to remove it from the market. In contrast, before being allowed to market a drug product, a manufacturer has to obtain FDA approval by demonstrating convincingly that the product is both safe and effective. You've probably been through this kind of argument before, and you say, "Well, even if something's on the market, haven't we seen examples of drugs that have been shown to be unsafe once they've been on the market, and aren't there more people who have adverse events associated with common drugs than with supplements?" This may be true, and you can certainly give examples such as Tylenol poisoning. But as you'll see in a minute, it is definitely comparing apples and oranges.

This is a label for a product that is actually now no longer on the market. Centrum marketed a line of herbal products for a little while. One of them was St. John's wort, but I'm using this as an example of what a dietary supplement label is supposed to contain by law. It has to give the name of the product. It can contain some kind of indication, some claim for what the product is there for. In this case, the claim is to help maintain healthy emotional balance and a positive outlook. With very few exceptions, a dietary supplement, by law, cannot make a claim to treat, cure, mitigate, or even prevent a disease. That's a disease claim, and it's almost exclusive property of drugs to be able to make those claims. Instead, supplements can make claims called structured-function claims. For example, that "these ingredients are intended to affect a structure of the body or a function of the body." A dietary supplement ingredient can't claim to reduce cholesterol levels, but it can say that it "maintains a healthy heart." It can't even technically say that it "maintains cholesterol in the normal range" because cholesterol implies a disease claim. It's created a lot of work for wordsmiths. The label can go on to

provide some other information for consumers, and some of the labels are really very informative if you can read them. I can only read this label when it's up on a screen like this. I couldn't possibly read it if I were looking at the bottle. There are some facts about the product that the manufacturer is expected to provide. In fact, this looks like a nutrition facts label on a food. That is deliberate because the supplement facts are intended to supplement the information that might be there from a food facts label. It also is supposed to indicate something about how the dosage was arrived at. It's supposed to indicate what other things are in there. It must also contain a disclaimer. This product had the following disclaimer on the back and on the front of the label: "These statements have not been evaluated by the U.S. Food and Drug Administration. The product is not used to diagnose, treat, cure, or prevent any disease." Those are the required elements of the label, and a manufacturer can put other things on as they wish.

If they're marketing a new product, the manufacturer's label has to at least be evaluated by the FDA in order to see that it doesn't make an unlawful health claim. These kinds of claims are the ones that you see for dietary supplement ingredients: ginkgo enhances memory; coenzyme Q10 boosts energy; glucosamine for healthy joints; St. John's wort enhances mood and temperament; or vitamin E for the heart. You can't say that vitamin E cures heart disease or prevents heart disease, but you can say that it is "for the heart." Consumers usually know what is being referred to.

How many people use supplements? It varies depending on how the questions are asked, when they're asked, and under what kind of circumstance. The National Health and Nutrition Examination Survey (NHANES) has been an ongoing measure of Americans' health habits for quite a number of years now. Newer data will be coming out shortly. In that survey, which was taken around the time that DSHEA was passed, about 1/2 of all Americans used supplements on a regular basis. It constitutes about 100 million people. This number has been remarkably robust, actually. Usually, a little over 1/2 of Americans in most surveys are reported to be taking supplements of one sort or another. Most of them, about 2/3**,** are taking vitamins or minerals or both on a regular basis. But fully 1/4 of Americans in 1998, perhaps slightly fewer now, had been taking at least one herbal

supplement. Users are predominantly adult women. About ½. Adult men use dietary supplements at a somewhat slower clip. Why? Mostly for indications that you're familiar with: to feel better; to prevent illness; to improve recovery when sick; to build strength and muscle; to follow the doctor's suggestion to take supplements; to live longer; or to lose weight. Which of those would be illegal reasons for somebody to market a dietary supplement? Feeling better is probably okay, but preventing illness, that's automatically precluded by the DSHEA. The manufacturer can't say that it will prevent illness, but you know that that's what it's for. There's nothing to stop consumers from using products that are on the market for any purposes; it just prevents the company from making a claim that it will prevent illness or that it will improve recovery when sick. That's mitigating an ongoing disease. Depending on whether you think that obesity is a disease, this might or might not be a disease claim.

It is, I think, the exception rather than the rule that doctors will suggest that their patients take supplements beyond vitamins and minerals. It may be more common now. We don't have data that are informative enough at this point to know for sure. But there is something of a disconnect between the physician and the patient when it comes to the use of supplements.

What do people use as information sources about supplements? Books, magazines and newspapers, physicians, health food stores, friends, pharmacists, and the Internet. Which ones do they think are reliable? Government agencies are way down on the list in terms of their information content for consumers when it comes to supplements. In one survey conducted in 2000, 75% of respondents reported that friends and family were the most reliable sources of their information, with newspaper or magazine articles coming in distant second. Only the Internet was less reliable than government agencies; I think that reveals something about what we do.

But perhaps the more relevant piece of information is that people, consumers, are really looking for information to support their decisions to take or not take supplements. About 2/3 of Americans feel quite confused about the value of supplements. There's conflicting

information. This survey was conducted by an organization called the Council for Responsible Nutrition, which is a trade association that represents the dietary supplement industry. Now, the trade association used this to support their aggressive move to develop information that they felt would be valuable for consumers, and I would agree with that. We might disagree about the content or the interpretation to be placed on the value, but I think it's fair to say that people probably need more information than they've been getting about supplements.

Here's one example: picture an interaction between a patient and his doctor. The doctor asks the patient, "Are you taking any medications?" The patient tells her that he's only taking a vitamin supplement, ginkgo, St. John's wort, and glucosamine sulfate. We don't think of these as medications. Unfortunately, doctors don't always ask the question in a way that probes for whether or not their patients are taking dietary supplements. This is important because one of the potential sources of harm associated with taking some supplements is when they're taken in combination with some drugs.

A lot of people take herbal products. Now this is slightly deceptive. Remember I said before about 1/4 of Americans reported taking herbal supplements on a regular basis? Of those, this survey identified that about 1/3 were opting to take herbal products in place of prescription medications. It also meant that they were taking them without very much advice from their physician. That should be cause for some concern unless people are very highly educated about the consequences of self-care with herbal products; it is a number that one needs to be concerned about. We should also be concerned that nearly as many people reported taking herbal products along with prescription products. We hope that they're doing that with the advice of a physician or some other health care provider, but that rate of use should still be cause for concern. Are people actually doing this in consultation with their physicians?

I need to explode a couple of myths. Just because something is natural doesn't mean that it's safe, that goes without saying. But how much do you believe that? There is a sense of wanting to take natural products in order to avoid the complications and problems

associated with synthetic medications. Sometimes it's the right thing to do. But the one does not equate with the other. Likewise, use of a product for thousands of years does not mean it's effective or safe. Frankly, it doesn't mean that thousands of years of use in a traditional healing system has anything to do with the way people use products like this in current western, usually American, life. One of the great examples is ephedra, which has been touted for weight management and athletic performance enhancement. Do you think that these were the indications for use in traditional Chinese medicine? No, they weren't. The traditional Chinese medicine indications for use of ephedra (Ma huang) were to relieve upper nasal congestion in an acute way. It was not for chronic management of weight or for athletic performance enhancement. There is nothing in traditional medicine that you can use to support that.

Another thing that needs to be clarified is that an herb as a plant is not the same as the ingredient, necessarily, in a capsule or a tablet. It could be better in a capsule or a tablet, and I can think of some examples where that's likely to be true, but don't assume it. It is quite possible that the beneficial action of something in a plant is precisely because it's in a plant matrix and not in a gelatin capsule. The last piece of information is that all brands of herbs are not the same. You can see 10 different St. John's wort preparations or echinacea preparations on the shelf; you can't be assured that they are all of equivalent value or that they even contain the same parts of the plants that they purport to contain.